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INGREZZA® (valbenazine) capsules and Hypersensitivity in Chorea Associated with Huntington's Disease

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the potential effects of INGREZZA and hypersensitivity.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with chorea associated with Huntington's disease (HD).[1]

Please review the separately attached INGREZZA FDA-approved Full Prescribing Information and Important Safety Information, including a Boxed Warning.

The INGREZZA FDA-approved Full Prescribing Information states:[1]

> **CONTRAINDICATIONS**
> INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.
>
> **WARNING AND PRECAUTIONS**
> **Hypersensitivity Reactions**
> Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in the post-marketing setting in patients after taking the first or subsequent doses of INGREZZA. A case of angioedema involving the lips and face, with rash and shortness of breath was reported in a patient with Huntington's disease taking INGREZZA during a clinical study. Urticaria and rash were also reported during a clinical study in patients with Huntington's disease. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA.

Clinical Study Results:

In KINECT®-HD, the Phase 3, double-blind placebo-controlled study to evaluate the safety and efficacy of valbenazine for the treatment of chorea associated with HD, adverse events of urticaria, rash, angioedema, and pruritus occurred in the valbenazine (VBZ) group and pruritus in the placebo (PBO) group (**Table 1**).

Angioedema was reported in 1 patient in the VBZ group and was a serious adverse event. The angioedema was considered by the investigator to be unlikely related to study treatment (likely cause, shellfish allergy) and resolved within a day. The patient continued treatment and completed the study on 80 mg.[2]

Table 1: KINECT-HD TEAE

	Placebo (N=63) n (%)	Valbenazine (N=64) n (%)
Urticaria	0	6 (9.4)
Rash	0	5 (7.8)
Angioedema	0	1 (1.6)
Pruritus	1 (1.6)	1 (1.6)

The most common treatment-emergent adverse events (TEAEs) with valbenazine in the KINECT-HD study were somnolence and fatigue.[2]

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KINECT-HD2, is an ongoing Phase 3, open-label rollover study to evaluate the long-term safety and tolerability of valbenazine for the treatment of chorea associated with HD. Full results and analysis of this study is expected once the study is complete, early 2024.

Postmarketing Experience:

As the Prescribing Information states, "hypersensitivity reactions (including allergic dermatitis and pruritus) and cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in the post-marketing setting in patients after taking the first or subsequent doses of INGREZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."[1]

IMPORTANT SAFETY INFORMATION
Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

CONTRAINDICATIONS
INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA.

WARNINGS & PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA.

Somnolence and Sedation
INGREZZA can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism

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INGREZZA may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Furr Stimming E, Claassen DO, Kayson E, et al. Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled controlled trial. *Lancet Neurol.* 2023;22(6):494-504.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.